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Original Article

Effects of cold exposure on autonomic changes during the last rapid eye movement sleep transition and morning blood pressure surge in humans

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ABSTRACT

Background: Various studies have linked the occurrence of cardiovascular events and low ambient temperatures as well as the morning blood pressure surge (MBPS). We hypothesized that low ambient temperatures produce a higher sympathetic change during the last rapid eye movement (REM) sleep transition and that this may play an important role in cold-related cardiovascular events.
Methods: All experiments were carried out on 12 healthy male adults, aged 24.00 ± 0.74 years, who participated in two experimental conditions randomly (>1 day apart): warm (23 °C) and cold (16 °C). Blood pressure (BP) was measured every 30 min for 24 h by autonomic ambulatory BP monitoring. The electroencephalograms, electrocardiograms, ambient temperature, near-body temperature, and physical activity were recorded by miniature polysomnography for 24 h.
Results: The cold conditions resulted in: (i) higher MBPS than under warm conditions; (ii) significant and greater sympathetic index changes during the sleep–wake transition than during cover-to-uncover and supine-to-sit position tests; (iii) the non-REM–REM transition-related sympathetic elevation during the cold conditions being significantly higher in late sleep period than in early sleep period; (iv) at 1 h prior to morning awakening, the value of total power of heart rate variability changes being significantly negatively correlated with the changes of near-body temperature; and (v) significantly higher arousal index and shorter average interval of REM periods than in warm conditions.
Conclusion: Cold exposure elevates the amplitude of MBPS and is associated with late sleep stage transition sympathetic activation, which might have important implications for cold-related cardiovascular events.

1. Introduction

Many cardiovascular disease events occur more frequently on winter mornings [1,2], and a low ambient temperature has been regarded as a major contributing factor [3]. The peak incidence of many cardiovascular events is at the end of the sleep period and prior to morning awakening, compared to any other period of the day [4–6]. A higher number of arousals and longer rapid eye movement (REM) stage duration always occur during this period [4,6]. Neuronal control of the cardiovascular system – a possible etiology [7,8] – also changes markedly in association with these sleep structure changes [9,10]. Therefore, the interaction between cold, sleep, and the autonomic nervous system (ANS) may be involved in these cold-related cardiovascular events.

The morning blood pressure surge (MBPS) is an acute blood pressure (BP) change that occurs during the sleep–wake transition in the early morning. This is a normal physiological phenomenon, but an exaggerated change is likely to be a risk factor for the development of a cardiovascular event [11–13]. Several lines of studies have demonstrated a link between the occurrence of cardiovascular events and a low ambient temperature as well as the MBPS [14]. Thus, with regard to BP measurements, ambient temperature is an important factor, particularly the personal-level environmental temperature [15]. It is well known that BP variation is strictly regulated within a narrow range by the ANS. Decreased

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parasympathetic activity together with increased sympathetic activity is thought to cause cardiovascular abnormalities [11,16,17]. Consequently, autonomic dysfunction is likely to result in disruptive BP fluctuations, which would then present as an exaggerated MBPS. Although Taiwan has a subtropical climate, nevertheless cardiovascular events still occur more frequently in winter than during any other season [18–20]. However, the effects of ambient temperature change, ANS, and late sleep stage transition on the MBPS have not been established conclusively. Even though there have been no reports associating ambient temperature during winter in Taiwan with cardiovascular events, a climate model that mimics the winter season in Taiwan was established in order to study the mechanisms related to cardiovascular events in this context.

The application of heart rate variability (HRV) analysis to freely moving humans and animals has recently gained popularity as a means of quantifying ANS functioning non-invasively [21–24]. Spectral analysis of the HRV by Fourier transformation has been categorized into high-frequency (HF) and low-frequency (LF) powers. HF is considered to represent vagal control of heart rate [21,25], whereas LF% and the LF/HF ratio are considered by some investigators to reflect sympathetic modulations or alternatively to mirror the sympathovagal balance [21–24].

However, up to the present there has been no investigation targeting ANS index changes during sleep stage transitions in a cold environment. In this study, we used a cold ambient temperature to induce an exaggerated change in the MBPS and to explore sleep architecture changes and sympathetic activation during the late sleep stage transition. Therefore, in this study, our aims were: (i) to determine whether a cold ambient temperature may cause an exaggerated change in MBPS and may also affect sleep-architecture-related sympathetic activation, particularly during the late sleep stage transition; and (ii) to investigate the effects of personal-level environmental temperature, which has been replaced by near-body temperature (NBT) in this study, on the MBPS, on autonomic functioning during the sleep period, and on postural state change measurements after morning awakening.

2. Methods

2.1. Subjects

Twelve healthy male adults with a mean age 24.00 ± 0.74 (mean ± SEM) participated in this study. They were volunteers recruited from a university student population. All subjects were in good health, normotensive, had a body mass index between 18 and 24 kg/m^2, had regular sleep/wake patterns, were on no medications, and had no history of smoking or drinking alcohol. The subjects' demographic data are presented in Table 1. None of the participants had any history of psychopathology or any medical condition known to influence sleep or ANS functioning. All subjects gave written informed consent after taking part in the experimental procedures, which were fully described to them. The procedures used in this study were approved by the Institutional Review Board of National Yang-Ming University.

Table 1
General measurements and blood pressure values during baseline recording under the two ambient temperature conditions.

	Warm conditions (n = 12)	Cold conditions (n = 12)
General measurements		
Age (years)	24.00 ± 0.74	
Height (cm)	172.18 ± 1.23	172.18 ± 1.23
Weight (kg)	65.43 ± 1.53	65.26 ± 1.61
BMI (kg/m^2)	22.07 ± 0.48	22.02 ± 0.53
PSQI	5.08 ± 0.42	
Baseline recording		
SBP (mmHg)	119.01 ± 2.77	123.08 ± 2.37
DBP (mmHg)	75.03 ± 2.72	80.44 ± 1.76*

BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values are mean ± SEM (n = 12), estimated by calculating the average values of five data points from 21:30 to 23:30. The period of baseline recording was from 21:30 to 00:00. DBP during baseline recording under cold conditions was significantly greater than under warm conditions.
* $P < 0.05$.

2.2. Subjective measures

Subjective sleep quality and sleepiness were assessed before and following the cold and warm conditions. Four mood variables – depth of sleep, difficulty going to sleep, difficulty staying awake, and sleepiness/awakeness during the waking period – were assessed using 100 mm visual analogue scales (VAS). Higher VAS scores indicated bad sleep quality and bad alertness during the awakening period. Sleepiness was assessed using the Stanford Sleepiness Scale (SSS), which is a seven-point Likert-type scale. The SSS score was evaluated hourly. Higher values indicated higher levels of sleepiness, ranging from alert to very sleepy (score: 1–7).

2.3. Data acquisition

Electrophysiological signals were recorded by a miniature physiological signal recorder (TD1, Taiwan Telemedicine Device Company, Taiwan) [25–27], carried by each subject. The small size (5.2 × 3.1 × 1.2 cm) and light weight (11 g) of the recorder produced a minimum interference on the participants. The recording of the electrophysiological signals was a simplified version of standard sleep monitoring [28], with only four electrophysiological signals [electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG)], two temperature signals, and physical activities signals (ACT) being recorded. There were only four channels for electrophysiological analysis and sleep scoring; nevertheless many datasets gathered through four channels have been published [26]. EEGs were recorded from the C3 point with a reference point at A2 [29]. EOGs were recorded from a pair of differential electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus [28]. The EOG recordings were able to detect both horizontal and vertical movements of the eye ball in one single channel of recording and are have been widely used in sleep research. EMGs were recorded from a pair of differential electrodes on the submental area. ECGs were recorded from V5 site on the chest. Room temperature was maintained at either 23 °C or 16 °C by central air-conditioning. The heat-sensitive sensor was placed on the forehead and extended into air for recording room temperature. A previous study revealed that the personal-level environmental temperature was an important predictor of BP values [15]; thus the other sensor – surrounded by styrofoam for heat insulation – was placed on the chest for measuring the subject's heat transition resistance 4.0 mm from body skin. We reasoned that recording the changes in NBT between the human body and bedcover may be useful for estimating BP and assessing autonomic function.

A BP recorder (WatchBP™ Home Blood Pressure Monitor, Microlife, Taiwan) was programmed to collect data at 30 min intervals for 24 h. The cuff was placed on the left upper arm. This study was started from 21:30 and lasted for 24 h. The subjects were required to wear identical clothing provided by us [30]. The subjects also filled out the SSS and VAS assessments in order to rate self-feelings about the experimental condition every hour. The acquired data were stored on a flash memory stick for subsequent

off-line analysis. The EEG, EOG, and EMG signals were used for sleep scoring, and the ECG signal was used for HRV analysis.

2.4. Experimental design

All subjects were randomized to undergo the two different experimental conditions: warm (23 °C) and cold (16 °C). The two experiments took place at least more than one day apart. Subjects were requested to abstain from caffeine and alcohol, and were not permitted intense activity during the entire study. During each trial period, participants were asked to maintain their regular sleep schedule. The recording started at 21:30 and lasted for 24 h. Subjects were asked to complete a sleep questionnaire (Pittsburgh Sleep Quality Index, PSQI) and their participation consent form prior to participating the study. During the recording period, subjects were allowed to undertake a whole night of sleep in the sleep laboratory (Sleep Research Center, National Yang-Ming University, Taiwan) inside a sound-attenuated room with a temperature of 24.40 ± 0.78 °C and humidity of 55–60% in warm conditions, and with a temperature of 16.67 ± 0.45 °C and humidity of 55–60% in cold conditions. The experimental procedure included baseline recording (from 21:30 to 00:00), a whole-night sleep study (from 00:00 to 07:30), and a cover-to-uncover supine-to-sit test (from 07:30 to 08:30). In the baseline recording, subjects were allowed to stay awake. They could use a computer (excluding games), listen to music, and watch movies. During the whole-night sleep study, subjects were requested to lie down in a supine position and cover themselves with a quilt. After morning awakening, subjects went through the body position changing test, which consisted of cover-waking test (CW), uncover-waking test (UCW), and supine-to-sit test (Sit). A period of free-moving time was allowed between 09:00 and 21:30. Previous studies have shown that clothes are important for thermal comfort [30]. Thus, the subjects wore identical clothes and bedcover during the sleep period to maintain the same level of thermal comfort. Participants were requested to abstain from caffeine and alcohol 3 days before and during the entire study. Participants were requested to finish the last meal at the time-period between 18:00 and 19:00. Participants were also requested not to take hot water, soup, drinks and spicy foods during the study period. We also measured the personal ACT and requested participants not to perform intense exercise during the entire study. At no time did we inform participants about measurement of the temperature between bedcover and human body, but the participants were requested to wear the same clothes and use the same bedcover provided during the entire study. The personal ACT were also compared between conditions. There were no differences in such factors for the same subject between the two different study conditions and across all subjects for the same conditions.

2.5. Signal processing

To analyze the HRV, a special computer program in Pascal language (Borland Pascal 7.0, Borland, Austin, TX, USA) was designed. The detailed procedures of the computer program are as follows. Preprocessing of the ECG signals was according to the recommended procedures [23] as detailed in our previous investigations [24,29]. In brief, the computer algorithm identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood using a standard QRS template. Stationary R–R intervals (RR) were resampled and linearly interpolated at a rate of 64 Hz to provide continuity in the time domain.

2.6. Accelerometery

Acceleration values were stored in the flash memory for each axis, namely x (mediolateral), y (vertical), and z (anteroposterior). Each axis had a sampling frequency of 125 Hz and could detect accelerations ranging from −3 to 3 cm/s^2. A vectorial magnitude was calculated as

$$\sqrt{x^2 + y^2 + z^2}.$$

The quantified magnitude of ACT was estimated by calculating the root mean square of the vectorial magnitude for each time-period (epoch).

2.7. Power spectra analysis

The amplitudes of the heart rate variations were measured in the frequency domain using power spectral analysis. The RR signals to be analyzed were truncated into successive 64 s (4096 points) time-segments (windows or epochs) with a 50% overlap. A Hamming window was applied to each time-segment to attenuate the leakage effect [31]. Our algorithm then estimated the power density of the spectral components based on fast Fourier transformation. The resulting power spectrum was then corrected for attenuation resulting from the sampling and the application of the Hamming window [24].

For the HRV analysis, mean RR, total power (TP), low-frequency (LF, 0.04–0.15 Hz), the low-frequency to high-frequency (0.15–0.4 Hz) power ratio (LF/HF), normalized LF (LF%), and high-frequency power (HF) were quantified [23,24]. The TP, LF, HF, and LF/HF were logarithmically transformed to correct for their skewed distributions [24].

2.8. Sleep scoring analysis

For sleep stage analysis, the data file was converted into European Data Format [32] and was then imported into a sleep analysis software program (Somnologica 3.1.2, Embla, Denver, CO, USA). Computer-assisted sleep analysis was carried out according to the criteria defined by Rechtschaffen and Kales [28] and revised by the American Academy of Sleep Medicine (AASM). The results were verified by a qualified sleep technician [32]. The definition of sleep cycle was composed of NREM sleep and the subsequent REM sleep. The duration of successive cycles was defined based on NREM stage 2 or REM onset, usually 90 min per cycle and commonly four or five cycles in whole-night sleep. Sleep architecture was divided into four cycles: cycles 1 and 2 were in the first half of sleep, and cycles 3 and 4 were in the second half.

For sleep transition analysis, the transition point was defined by the last epoch of NREM sleep followed by the first epoch of REM sleep. The timing of the first epoch of REM sleep for the NREM to REM sleep transition point was recorded, and the sympathetic activity and parasympathetic activity were analyzed before and after sleep transition.

2.9. Statistical analysis

All data are presented as mean ± standard error of the mean. The differential average values were calculated for the time-period 1 h before and after morning awakening to evaluate the level of MBPS and changes of HRV under the two conditions. We defined 00:30–03:30 as the first half of sleep and 04:00–07:00 as the second half of sleep for evaluating the changes of SBP, DBP, NBT, and ACT. The differences in HRV indices among cycles were evaluated by estimating average values for each cycle period. After morning awakening, changes in BP, temperatures and HRV parameters were estimated by calculating the differential average values between the latter and former states, which included CW minus Sleep, UCW minus CW, and Sit minus UCW (Sleep: 1 h before the morning awakening;

CW, UCW and Sit: 20 min during the state period). The analysis of the difference between the cold and warm conditions was carried out by paired *t*-test. One-sample *t*-tests were used to analyze the differences between the delta value and baseline. The effects of the two factors (ambient temperature and sleep stage) on changes of autonomic activities were assessed by two-way mixed design ANOVA (two ambient temperatures × two sleep stages) [33]. When pinpointed by a significant *F*-statistic, the differences between states were isolated using post hoc comparisons and Fisher's least-significant difference test. As LF% in cycle 2 in warm conditions was not normally distributed, the comparisons of LF% between cycle 2 and cycle 3 were assessed by Friedman two-way analysis. When a statistically significant interaction was identified, simple main-effect analysis of factor was applied. The correlation between changes in autonomic activities and NBT was examined by a simple linear regression model. $P < 0.05$ was considered significant.

3. Results

3.1. Exaggerated MBPS and sympathetic changes under cold conditions

During baseline recording, DBP in cold conditions was significantly higher than under warm conditions (Table 1). The mean ambient temperatures in cold and warm conditions were 16.67 ± 0.45 °C and 24.40 ± 0.78 °C, and the mean difference between the two conditions was 7.73 °C ($P < 0.001$). Higher RR, HF and NBT together with lower LF/HF and LF% values were prominent during the night of sleep (from 12:00 to 07:30) than during waking (from 07:30 to 09:00); in parallel, lower RR, HF and NBT values together with higher LF/HF and LF% values were found during waking compared to sleep. When the participants were in the sleep laboratory (21:30 to 09:00), the ambient temperature was kept within a narrow range (Fig. 1, Ta, lower panel). The NBT and Ta did not show a circadian rhythm of skin temperature throughout the study period, confirming that NBT and Ta measurements were not contaminated by skin temperature.

Fig. 2 demonstrates that the diurnal patterns of BP, NBT and ACT started at 09:00 and lasted for 12 h under cold and warm conditions. Sleep time 00:00 was 07:30. There were significant increases in SBP and DBP and decreases in NBT after awakening in cold conditions whereas there was no significant difference in ACT during sleep period and after awakening (Fig. 2A). The NBT values were not significantly different between cold and warm conditions in first half ($P = 0.486$) and second half ($P = 0.640$) of sleep. In addition, ACT values were not significantly different between cold and warm conditions in the first half ($P = 0.865$) and second half ($P = 0.117$) of sleep (Fig. 2). The average BP values recorded during the sleep period (00:00–07:30) and during morning time (07:30–08:30) under cold conditions are displayed in Figs. 2B and 3A. Under cold exposure, the SBP and DBP during the MBPS were significantly greater, and NBT was significantly lower than in warm conditions ($P < 0.05$), whereas the ACT was not significantly different during this period. These results revealed that different ambient temperatures had noticeable effects on NBT changes, possibly affecting MBPS. Significant changes in HRV indices, excluding TP, in cold conditions as well as HF and LF in warm conditions, indicated that ambient temperature had a significant effect on ANS functions, whereas there were no significant differences between the two conditions in HRV indices during the MBPS period.

3.2. Possible factors that might increase the MBPS in the morning under cold conditions

Ambient temperature during the entire study in our sleep laboratory room remained steady (Figs. 1 and 4A). As expected, NBT was significantly decreased under cold conditions for cover-to-uncover state than warm conditions; nevertheless, it trended to steady in other time-periods (Figs. 2 and 4A). The changes in SBP, DBP, RR, LF, TP, LF/HF, and LF% under cold conditions and in RR and LF% under warm conditions between sleep and wake were significant (Fig. 4). There was a notable change between warm and cold conditions on HRV index except TP and HF. Four further significant changes were noted: DBP ($P < 0.05$) increased under warm and cold conditions for cover-to-uncover state changes, and these were SBP ($P < 0.05$) and DBP ($P < 0.05$) under cold conditions for supine-to-sit position change. However, the HRV parameters changed insignificantly at the same state and position changes (Fig. 4B). There was a significant temperature change by state change interaction for the changes in LF, LF/HF, and LF%. For the sleep–wake transition under a similar situation, BP values, HRV values, ΔRR, ΔLF, ΔLF/HF, and ΔLF% were significantly different between the two conditions (ΔRR, $P \leqslant 0.05$; ΔLF, $P < 0.05$; ΔLF/HF, $P < 0.05$; ΔLF%, $P < 0.05$), but these effects were not observed under other conditions (Fig. 4B). Thus, both sleep–wake transition and posture state changes are involved in cold-related exaggerated MBPS, during which the sleep–wake transition, not NBT change, was involved in the majority of effects on changes in HRV indices in cold conditions.

3.3. Exaggerated sympathetic changes during the NREM–REM transition during the late sleep stage under cold conditions

The results of sleep stage scoring were used to analyze ANS activity over the whole sleep period. The whole night's sleep was divided into four cycles; for most of cycles 1 and 2, the subjects were in the range of the first half of the sleep period; for cycles 3 and 4, the subjects were in the range of the second half of the sleep period. Thus, the sleep stage was divided into two parts: one was the first half of sleep (cycles 1 and 2), and the other was the second half of sleep (cycles 3 and 4). Basal LF/HF and LF% during NREM and REM under cold conditions were significantly higher during the second half of sleep than during the first half of sleep (Fig. 5A), unlike HF. Furthermore, two-way repeated measures ANOVA tested whether sleep stage and ambient temperature conditions had significant impacts and/or interaction effects on these two factors. As LF% in cycle 2 in warm conditions was not normally distributed, the comparisons of LF% between cycle 2 and cycle 3 were assessed by Friedman two-way analysis. The results revealed a significant main effect with respect to the state changes in cycle 3 sleep for the changes in RR ($F = 10.436$, $P < 0.05$), TP ($F = 6.253$, $P < 0.05$), HF ($F = 2.238$, $P < 0.05$), LF/HF ($F = 19.517$, $P < 0.05$), and LF% ($F = 17.227$, $P < 0.05$). We found that REM sleep had a major effect on LF% and LF/HF compared to NREM sleep over the whole sleep period. In addition, we compared the differential NREM and REM stage values for these HRV parameters changes (Fig. 5B). The comparison of HRV indices is not shown, as the number of subjects was small in the last cycle even though the changes in sympathetic indices (LF/HF and LF%) seem to be greater than in former cycles. Thus, we performed further analysis of ANS activity during the sleep stage transition (during late sleep) using a small time-window (2 min before and 2 min after the NREM–REM transition point), which led the major change in ANS activity (Fig. 6A). An acute ANS activity surge under cold conditions was observed during the last NREM–REM transition but was not found during any other stage transition. The peak value highest recording point of the HRV parameter at 2 min after the NREM–REM transition was significantly higher than the value at 2 min before the NREM–REM transition (Fig. 6A). In Fig. 6B, ΔTP, ΔLF/HF and ΔLF% are seen to be significantly greater under cold conditions than under warm conditions. Furthermore, there is a significant SBP change during this

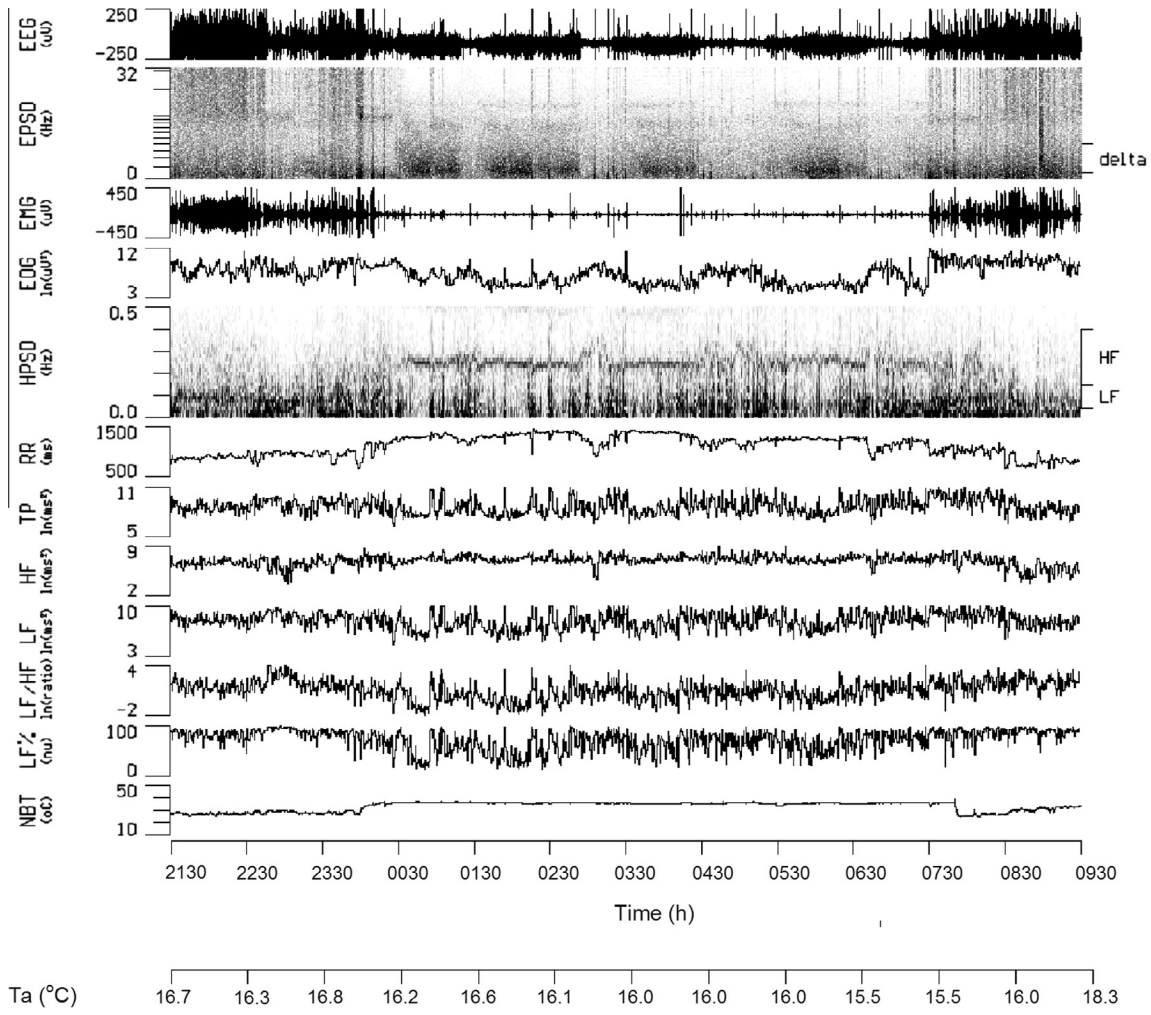

Fig. 1. Continuous and simultaneous analysis of a typical polysomnogram of a young male adult during night sleep (night sleep time: 00:00–07:30; real sleep time: 00:25–07:30) over 12 h of recording. There was a greater near-body temperature (NBT) variation after morning awakening than during sleep period. Electroencephalogram (EEG), electromyogram (EMG), electro-oculogram (EOG), power spectral densities of EEG (EPSD) and R–R intervals (HPSD), temporal alterations in mean R–R intervals (RR), the total power (TP), the high-frequency power (HF, 0.15–0.4 Hz), the low-frequency power (LF, 0.04–0.15 Hz), the LF–HF ratio (LF/HF) and the normalized low-frequency power (LF%) of the HPSD, NBT and ambient temperature (Ta, 1 h average) are also shown. Baseline recording: 21:30–00:00; the state change tests: 07:30–07:50 for covered-waking (CW) test, 07:50–08:10 for the uncovered-waking (UCW) test, 08:10–08:30 for the prone to sit (Sit) test.

sleep stage transition that only occurred under cold conditions, not in a warm environment (Fig. 6C).

3.4. Association between cold-induced ANS, sleep structure changes and cold-induced exaggerated MBPS

Correlations were calculated between HRV changes, MBPS, and NBT under cold and warm conditions. One hour prior to morning awakening, the differential values of NBT were negatively correlated with the changes in TP under cold conditions and under warm conditions (Table 2). We further analyzed a number of sleep characteristics to clarify the effect of cold ambient temperature on sleep architecture (Table 3). The average interval between REM episodes under cold conditions was significantly longer than under warm conditions, and the arousal index was significantly higher under cold than warm conditions. Furthermore, the results of subjective sleep quality and the emotional state of the subjects had no significant effect in relation to the two conditions, but the sleep difficulty level and awakening level after morning awakening under cold conditions trended to be lower and higher, respectively, compared to those under warm conditions (data not shown).

4. Discussion

In this study, portable miniature polysomnography was used to record EEG, EMG, EOG, ECG, NBT, ACT and ambient temperature in parallel with BP monitoring in order to clarify the possible role of sleep and ANS on cold-related MBPS changes. In the entire study, subjects were requested to wear the same clothes and use the same bedcover provided for the whole sleep period. Compared with warm conditions (23 °C), subjects in a cold ambient temperature (16 °C) showed an exaggerated MBPS and, at the same time, both sympathetic activity and heart rate were increased. Based on the presence of a cold-induced exaggerated MBPS, we therefore evaluated the change in ANS functioning in various different posture states after morning awakening. HRV indices showed a significant change during the sleep–wake transition under cold conditions; thus, the sleep–wake transition would seem to be a major factor affecting HRV and the MBPS when there is exposure to cold. We further clarified the possible factors affecting autonomic activity during the late sleep to morning period under cold conditions. In order to do this, we calculated the differential value for the last 1 h prior to morning awaking and identified factors showing a significant Pearson correlation between the TP changes and the NBT under the two temperature conditions (Table 2). This

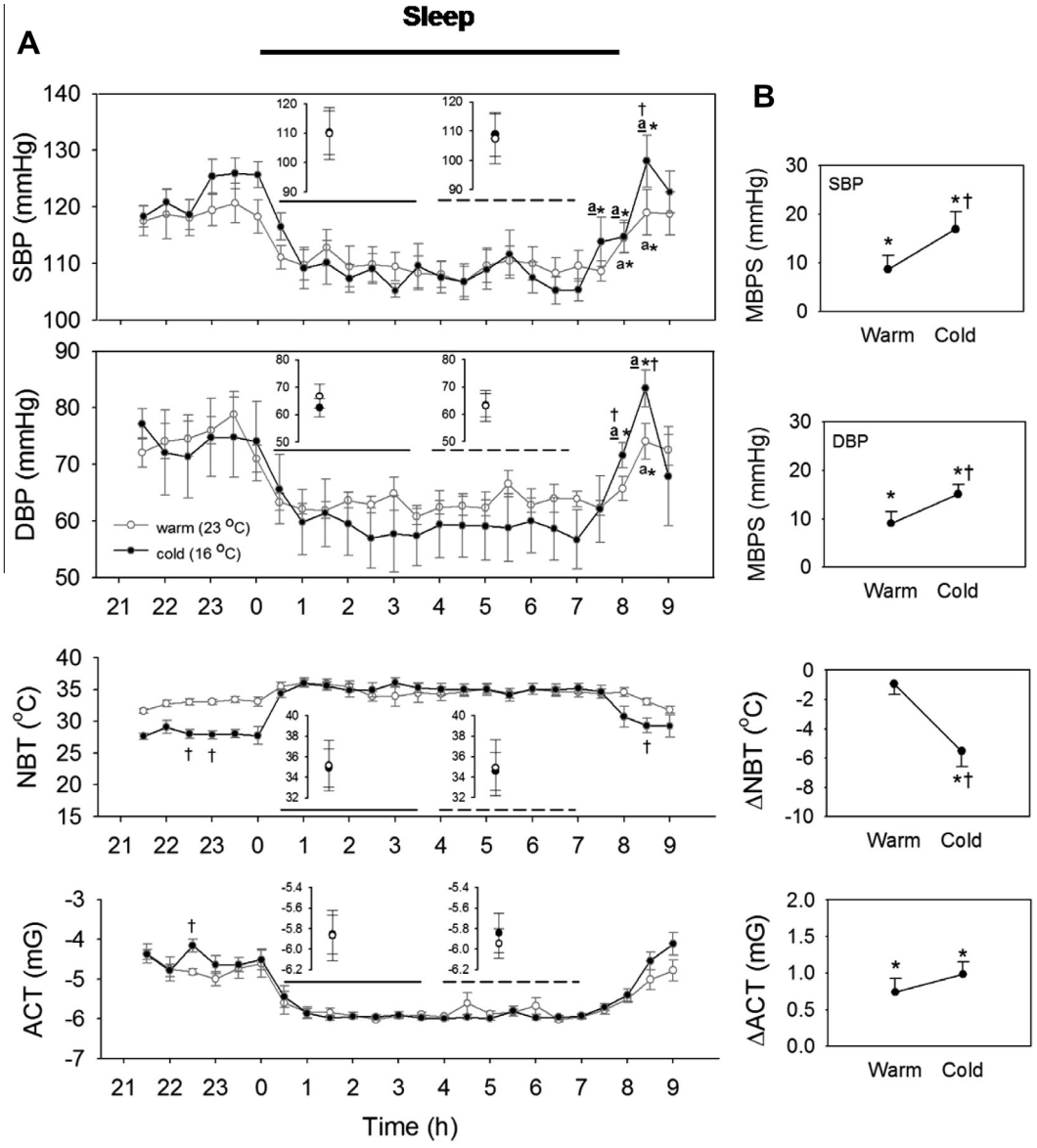

Fig. 2. Systolic blood pressure (SBP), diastolic blood pressure (DBP), near-body temperature (NBT) and physical activity (ACT) changes under cold and warm conditions for 12 subjects. (A) From 0:00 to 07:30 was the sleep time; after this period, there was a significantly exaggerated BP surge in cold conditions compared with warm conditions (SBP and DBP: one recording point/30 min; NBT and ACT: average values from 5 min before the BP data recording). The solid lines and dashed lines on inserts represent the time-period of first half of sleep and second half of sleep, respectively, and the plots preceding them represent the average BP values of these periods. The ACT values for the two conditions were not significantly different during whole sleep periods and after morning awakening. $^{*}P < 0.05$ vs average BP values in second half of sleep; $^{\dagger}P < 0.05$ vs warm conditions; $^{a}\underline{a}P < 0.05$ vs average BP values at 06:00–07:00 under warm and cold conditions, respectively. (B) Morning blood pressure surge (MBPS) for SBP and DBP as well as differential values of NBT and ACT between 1 h before and after awakening. $^{*}P < 0.05$ vs 0; $^{\dagger}P < 0.05$ vs warm conditions.

showed that NBT was important in terms of autonomic activity during late sleep close to the sleep–wake transition, even though there was no significant correlation with the MBPS. One possible explanation for this is that subjects in this study were healthy individuals. Additionally, although during the waking state the cover-to-uncover state was found to provoke an acute NBT change under cold conditions, no significant changes in ANS activity were found. However, autonomic changes were more prominent during the sleep–wake transition than during the significant changes in NBT during the cover-to-uncover transition or posture change on waking. This is the first new finding of the present study.

It is important to note that the second half of the sleep period before morning awakening is the peak time for many cardiovascular events [4,5,34]. Frequent sleep–wake transitions, a higher number of arousals and longer REM stage durations always occur during this period [4,6]. It is known that arousal from QS [6,35–38] and the transition from NREM to REM [6,39,40] may result in a significant BP change and sympathetic overactivity. According to a previous study, body temperature is able to affect ANS activity changes at sleep onset, and the sympathetic indices [LF/HF and LF/(LF + HF)] are known to change prior to the onset of each sleep stage [41]. However, the effect of a cold ambient temperature on the variation in ANS activity during the second half of sleep and the sleep transition has not been investigated in detail. Thus, in this study, we have focused on the baseline autonomic activity and autonomic changes that occur during stage transitions, especially during late sleep under cold conditions. Our results showed that, as sleep transits into its second half, sympathetic and parasympathetic activities are increased and decreased, respectively, and these changes occur irrespective of whether the individual is in

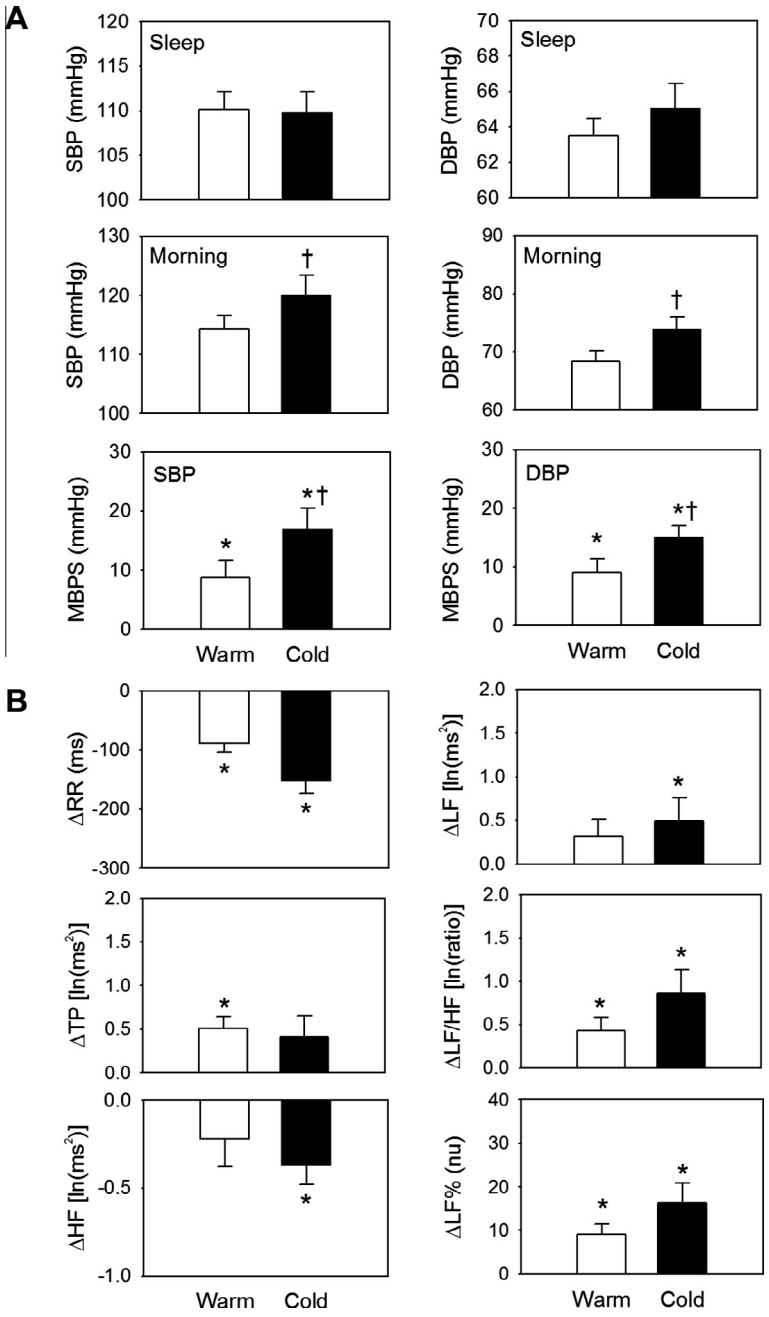

Fig. 3. Systolic blood pressure (SBP), diastolic blood pressure (DBP), morning blood pressure surge (MBPS) (A) and the values for the RR and heart rate variability (HRV) indices during the MBPS period (B) between the cold and warm conditions. Average values for MBPS and heart rate variability (HRV) were different between 1 h before and after awaking. $^{*}P < 0.05$ vs 0; $^{\dagger}P < 0.05$ vs warm conditions. RR, R–R intervals; TP, total power of HRV; HF, high-frequency power of HRV; LF, low-frequency power of HRV; LF/HF, low-frequency power to high-frequency power ratio of HRV; LF%, normalized low-frequency power of HRV.

REM or NREM sleep. However, a previous study [42], which choose 3, 10 and 17 °C for cold exposure conditions, found that the values for LF/HF decreased significantly during SWS (slow wave sleep) under 3 °C and 10 °C conditions compared to 17 °C. As compared to this study, cold exposure conditions of this earlier study are different and it seems likely that this might be the main reason for the different results. In the present study we targeted sleep stage transitions and showed that there was an acute rise in sympathetic activity during the NREM–REM transition preceding the last REM sleep under cold conditions, as well as that BP values also increased during the same period. Several studies have explored the effect of different sleep stages on various autonomic activities [43] and how ambient temperature conditions may influence sleep architecture [42,44,45]; nevertheless changes in autonomic functioning during sleep transitions have been lacking until now. Our results indicated an acute rise in sympathetic activity during the last NREM–REM transition under cold conditions, which is novel compared to previous studies. Cold exposure is an exogenous factor and cardiovascular events may occur during sleep when there is a sudden and acute elevation in sympathetic activity during cold conditions. The mechanism is unknown, but our findings should pave the way by providing a new direction to the study of sleep and cardiovascular events. A further important finding was that the arousal index (arousal number/min) under cold conditions

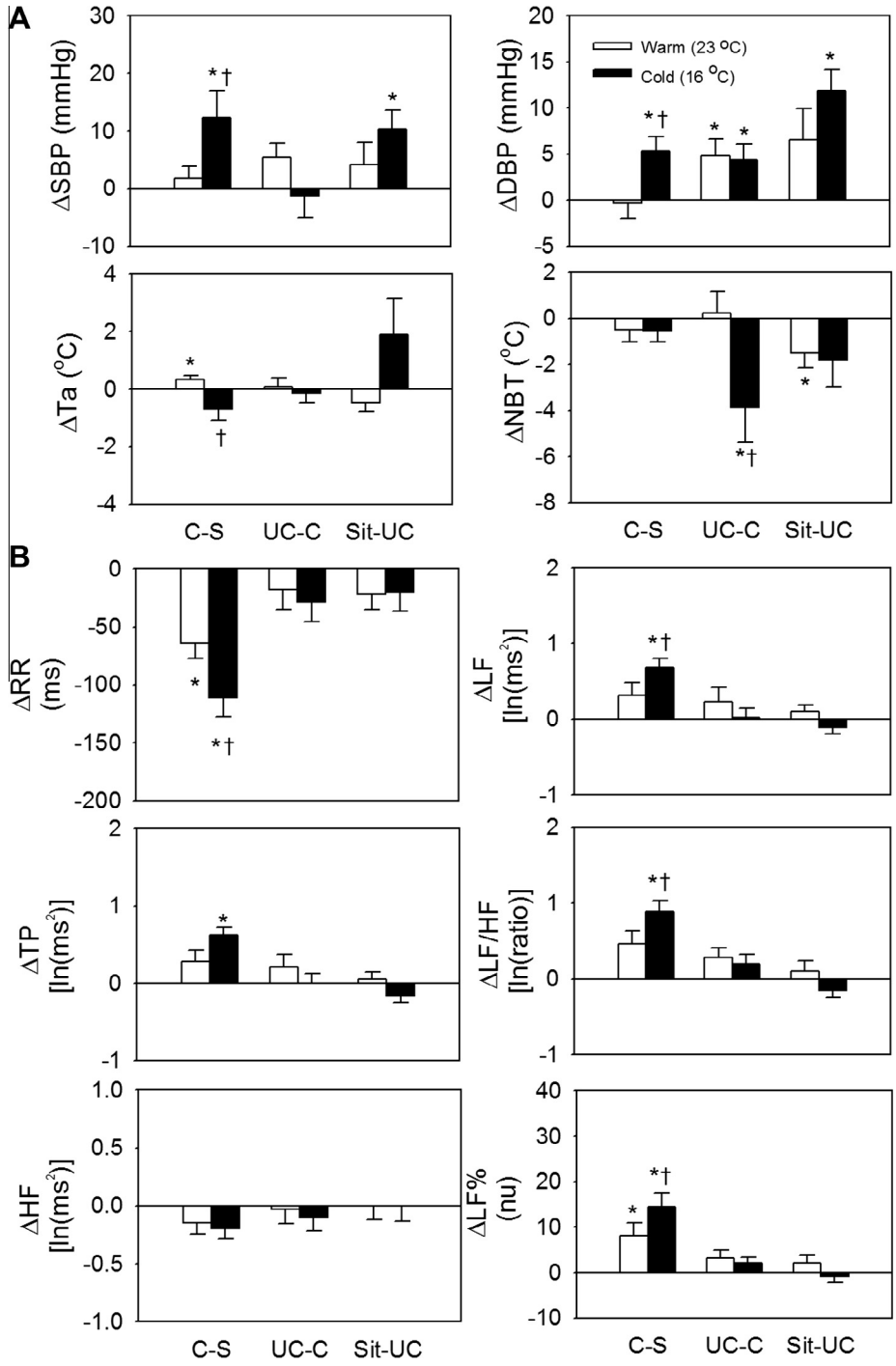

Fig. 4. Comparison of the changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), ambient temperature (Ta), near-body temperature (NBT) (A) and heart rate variability (HRV) parameters (B) between the cold and warm conditions for the state change tasks. Both the above values are average values for the covered waking state (C, 07:30–07:50) minus the average values 1 h prior to awake (C – S) under cold conditions are significantly higher than under warm conditions. The average BP at sit state (08:10–08:30) minus the average BP during uncovered waking state (Sit – UC) under cold conditions tended to be higher than under warm conditions. RR, LF, LF/HF and LF% were significantly different between the two conditions during sleep–wake transition. Additionally, NBT has a significantly change during cover-to-uncover state. RR, R–R intervals; TP, total power of HRV; HF, high-frequency power of HRV; LF, low-frequency power of HRV; LF/HF, low-frequency power to high-frequency power ratio of HRV; LF%, normalized low-frequency power of HRV; C, covered waking; UC, uncovered waking.

was significantly higher than under warm conditions. We believe that the rise in sympathetic activity associated with cold conditions may be related to the higher arousal number during the sleep period [46]. Thus the rise in sympathetic activity during the last NREM–REM transition under cold conditions is likely to be an important factor affecting sleep-related cardiovascular events. This is the second new finding of the present study.

The ambient temperature during winter in a subtropical zone, such as in Taiwan, is between 10 °C and 20 °C. This is not very cold; nonetheless, cardiovascular events are still significantly more frequent in winter than during other seasons in Taiwan [19]. Taiwanese people often leave a window opening to increase air flow in the bedroom, and this behavior results in a room temperature that is lower than when they use heating. Such behavior may

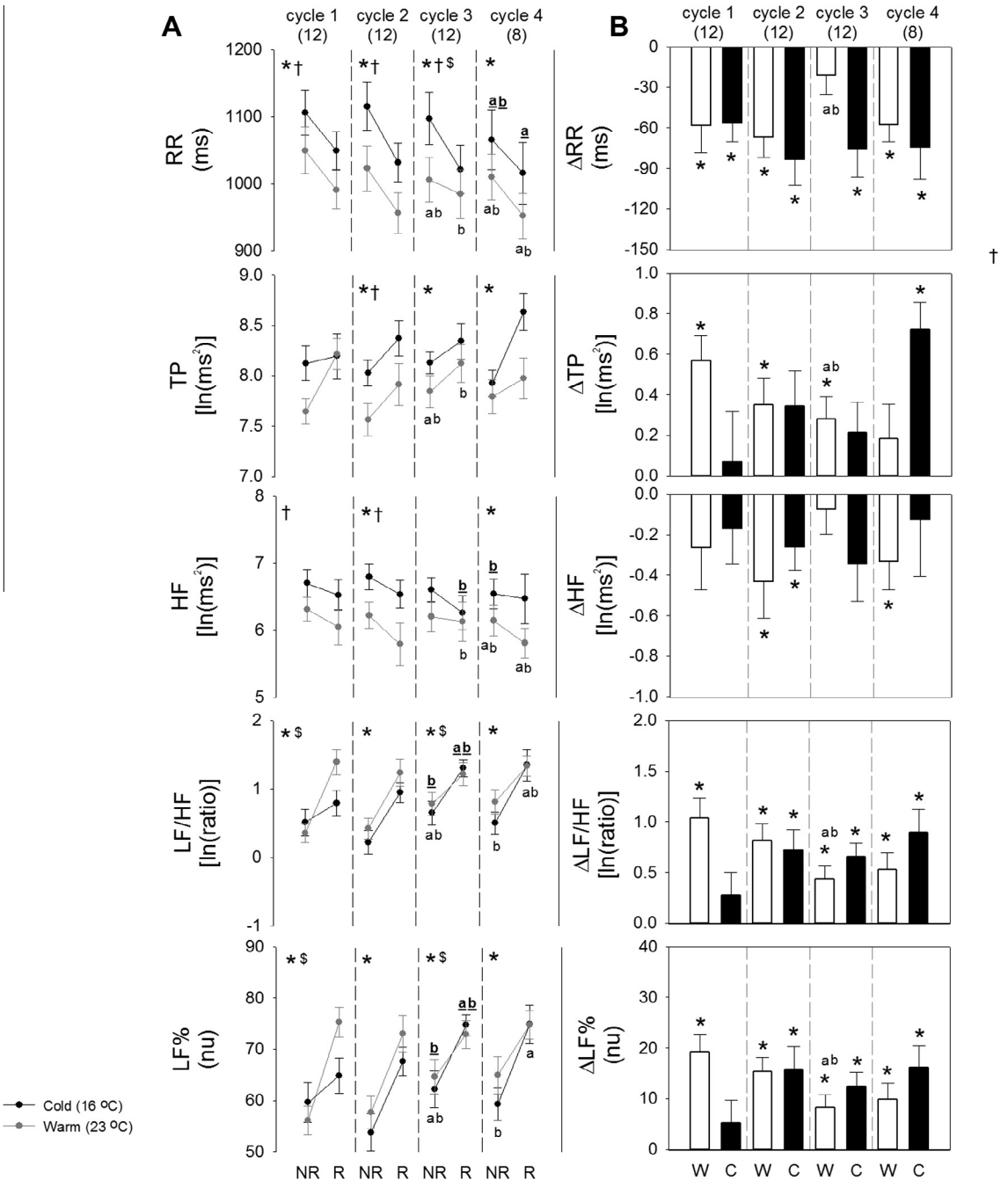

Fig. 5. Changes in autonomic activity during the different sleep cycles and the non-rapid eye movement (NREM)–rapid eye movement (REM) transition during the whole night sleep period. One-way and repeated measures analysis of variance (ANOVA) was used to test the differences across sleep cycles and two-way repeated measures ANOVA to test whether sleep stage and the ambient temperature condition had a significant impact and/or interaction effect between these two factors and autonomic activity. As LF% in cycle 2 in warm conditions was not normally distributed, the comparisons of LF% between cycle 2 and cycle 3 were assessed by Friedman two-way analysis. (A), Autonomic activity changes among sleep cycles. $^{*}P < 0.05$ vs NREM; $^{\dagger}P < 0.05$ vs warm conditions; $^{\$}P < 0.05$: interaction effect between temperature and sleep stage. $^{a}P < 0.05$ vs cycle 1 in warm conditions and $\underline{^{a}}P < 0.05$ vs cycle 1 in cold conditions; $^{b}P < 0.05$ vs cycle 2 at warm conditions and $\underline{^{b}}P < 0.05$ vs cycle 2 in cold conditions. $^{\#}P < 0.05$ vs NREM by Friedman two-way analysis; $^{A,\underline{A}}P < 0.05$ vs cycle 1 in warm and cold conditions by Friedman two-way analysis, respectively; $^{B,\underline{B}}P < 0.05$ vs cycle 2 at warm and cold conditions by Friedman two-way analysis, respectively. (B) Comparison of changes in heart rate variability (HRV) parameters between cold and warm conditions. $^{*}P < 0.05$ vs 0; $^{a}P < 0.05$ vs cycle 1 in warm conditions; $^{b}P < 0.05$ vs cycle 2 in warm conditions. $^{B}P < 0.05$ vs cycle 2 at warm conditions by Friedman two-way analysis. NR, NREM; R, REM; W, warm; C, cold; TP, total power of HRV; HF, high-frequency power of HRV; LF/HF, low-frequency power to high-frequency power ratio of HRV; LF%, normalized low-frequency power of HRV.

help explain why cardiovascular events are prevalent in Taiwan during winter despite its subtropical geography. In the present study, we chose 16 °C in order to mimic the ambient temperature during winter in Taiwan (the average ambient temperature during winter over the last three years has been 16.5 °C). Our results reveal that, in normotensive subjects, a temperature of 16 °C seems to result in a significant elevation in MBPS, greater sympathetic activation, and a prolongation of REM interval. This study is the

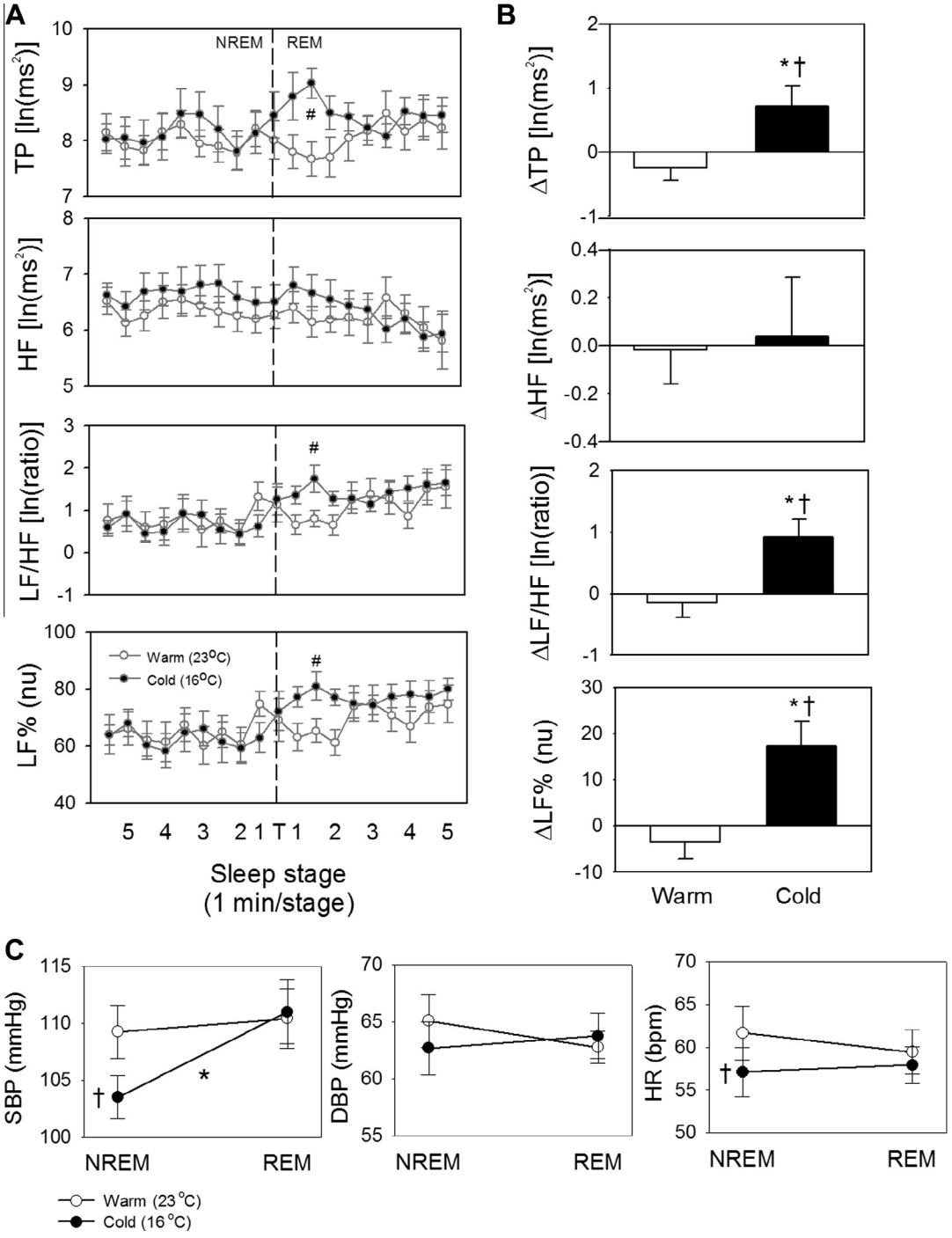

Fig. 6. Variation in heart rate variability (HRV) parameters during the last non-rapid eye movement (NREM)–rapid eye movement (REM) transition of second half of sleep. (A) Temporal variation of HRV parameters. Each plot was calculated by averaging the 1 min values. TP, total power of HRV; HF, high-frequency power of HRV; LF/HF, low-frequency power to high-frequency power ratio of HRV; LF%, normalized low-frequency power of HRV. (B) Comparison of changes in LF% and LF/HF (from 2 min before to 2 min after the NREM–REM transition) between cold and warm conditions. (C) Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) change in the last NREM–REM transition. $^{\#}P < 0.05$ vs the lowest points at 2 min prior to stage transition; $^{*}P < 0.05$ vs NREM; $^{\dagger}P < 0.05$ vs warm conditions.

first to investigate the possible role of ANS during winter in the subtropical zone, and this is the third new finding of the present study.

This study revealed that the magnitude of the average REM period interval was longer under cold conditions compared to warm conditions. Our findings support previous studies that have found the REM sleep interval to be longer at a cold ambient temperature compared to a warm ambient temperature (REM sleep tends to be longer at 13 °C than at 25 °C) [47]. However. other earlier studies have reported a reduction in REM sleep under cold conditions [45]. It is well known that thermoregulatory responses are impaired during REM sleep [48,49]; notwithstanding our results and those of pervious studies, both the difference in thermoregulation between cold and warm ambient exposure, and the role of thermoregulation in the various changes to sleep architecture, remain unclear. Nevertheless, in the present study there was a higher arousal index under cold conditions compared to warm conditions, which may be explained by the higher level of

Table 2
Correlation between changes in autonomic function and NBT at 1 h prior to morning awaking and MBPS under the two ambient temperature conditions.

	Warm conditions		Cold conditions	
	ΔTP	ΔNBT	ΔTP	ΔNBT
MBPS (SBP)	0.205 $P = 0.523$	−0.175 $P = 0.585$	0.015 $P = 0.962$	−0.024 $P = 0.940$
MBPS (DBP)	0.195 $P = 0.544$	0.128 $P = 0.692$	0.132 $P = 0.683$	−0.042 $P = 0.897$
ΔTP	1.000	−0.671 $P = 0.017^*$	1.000	−0.825 $P = 0.001^*$

NBT, near-body temperature; MBPS, morning blood pressure surge; TP, total power of HRV; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values were estimated by calculating the Pearson correlation values among MBPS and ΔTP as well as ΔNBT ($n = 12$). ΔTP was significantly negatively correlated with ΔNBT in cold and warm conditions.
* $P < 0.05$.

sympathetic activity present under cold conditions [42]. These topics deserve further study.

The most notable finding in this study was the fact that there are significant increases in LF% and LF/HF during the last NREM transit into REM stage under cold conditions, during which there was also a significant change in SBP. REM sleep prevails during the second half of sleep and it seems quite possible that the last NREM–REM transition prior to morning awakening might be the risk period for cardiovascular disease events.

However, as compared with warm conditions, the sleep depth score and the degree of wakefulness score tended to be higher under cold conditions compared to warm conditions. Although there was no significant difference in subjective sleep quality between the two conditions, one possible explanation may be that the subjects were in good health with regular sleep patterns, so that there was no significant effect of the cold ambient temperature (16 °C) on their subjective sleep quality; nevertheless, the cold ambient temperature did have a significant effect on autonomic functioning because it caused an exaggerated sympathetic activity change. Based on this result, we believe that cold conditions are not a factor that affects subjective measurements related to feelings, but rather that cold conditions do have a significant effect on ANS activity and the MBPS. This may be why protection against temperature changes during winter in Taiwan are usually ignored. Nevertheless, in the context of our results, it is important that people who live in a subtropical zone such as Taiwan are careful and take notice of ambient temperature changes during winter.

Table 3
Sleep characteristics under the two ambient temperature conditions.

	Warm conditions ($n = 12$)	Cold conditions ($n = 12$)
Arousal index	6.13 ± 0.83	7.80 ± 1.09*
Time in REM (min)	114.10 ± 9.65	102.75 ± 6.35
Time in N1 (min)	29.34 ± 4.31	26.88 ± 5.80
Time in N2 (min)	192.00 ± 12.59	205.63 ± 11.99
Time in N3 (min)	76.17 ± 5.78	77.83 ± 6.13
No. of REM periods	5.00 ± 0.48	4.08 ± 0.19
No. of SWS periods	4.67 ± 0.58	5.33 ± 0.51
Average interval between REM periods (min)	53.98 ± 3.90	70.56 ± 4.66*
Average interval between SWS periods (min)	67.64 ± 17.28	62.67 ± 9.70

REM, rapid eye movement; N, non-REM; N1 and N2, stage N1 and N2, belonging to the light sleep stage; N3, stage N3, belonging to SWS; SWS, slow wave sleep.
Values are means ± SEM ($n = 12$). There was a significant difference in arousal index and average REM interval between the cold and warm conditions.
* $P < 0.05$.

There are several limitations that may have affected this study. First, cold-induced cardiovascular events are known to occur more often in older, hypertensive subjects [50,51] and our study included young, healthy subjects. Thus, any extrapolation of the relationship between sleep characteristics, autonomic changes, and the MBPS to hypertensive patients and older subjects should be made with great caution. Second, some subjects underwent the experiments during July to September, which is a period of relatively hot weather in Taiwan. ANS functioning may have been affected by changes in circadian rhythm across the different seasons even though the ambient temperature of the experimental condition was well controlled. Third, the variation in ambient temperature across a single day and variation in ambient temperature from summer to winter may also be factors in cardiovascular events, but this study only dealt with a static ambient temperature. The effect of a variable or dynamic ambient temperature is well worth investigating in the future. Fourth, the present study may not have allowed enough time for acclimatization between different ambient temperatures before the cardiovascular and EEG measurements; thus, our findings are not appropriate to explain the effects of long-term cold ambient temperatures. Fifth, our data were gathered from only one EEG channel and this might have been insufficient for scoring sleep and identifying arousal events, especially when an EEG electrode falls off; nevertheless, we may point out that many results gathered through one EEG channel have been published elsewhere [25–27]. Sixth, the present study used only a single lower ambient temperature for testing, namely 16 °C, in order to mimic winter in Taiwan. This meant that no findings regarding the ideal temperature of each subject could be made. The scores for temperature sensation and thermal comfort were significantly lower under cold conditions compared to warm conditions ($P < 0.001$), with the lower temperature being interpreted by our subjects as feeling very cold and uncomfortable during cold exposure. Thus, in this study we were unable to explore the effects of a colder ambient temperature by making a comparison with each subject's ideal temperature. Seventh, the present study has only focused on the effects of cold ambient temperature during night time and sleep time, and we did not explore any effect that this might have had in relation to daytime activity. Finally, in this study, there were six subjects with PSQI > 5; nevertheless there were no significant differences between PSQI > 5 subjects and PSQI < 5 subjects for BP, RR during sleep and MBPS. In addition, none of the participants had any history of psychopathology or any medical condition known to influence sleep or ANS functioning. Nevertheless, we believe that the ideal temperature of each subject and the presence of poor sleep quality might have an important role to play in cardiovascular events, and we intend to clarify these important concerns in the future.

5. Conclusions

In this study we have confirmed that the effect of a cold ambient temperature on MBPS is greater than under warm conditions. A cold ambient temperature (even 16 °C) might have an important effect on the MBPS, on autonomic functioning during the stage transition in the second half of the sleep period, and on sleep architecture. An acute surge of sympathetic activity during the last NREM–REM transition is likely to have an impact on the occurrence of sleep-related cardiovascular events.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.03.022.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sleep.2014.03.022.

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